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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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WARNING LETTER

NOV 5 2004

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

FEDERAL EXPRESS

Maria L. Maccecchini, Ph.D.
President
Synthes BiomaterialsWorldwide Division
Synthes, Inc.
1230 Wilson Drive
West Chester, Pennsylvania 19380-4231

Dear Dr. Maccecchini:

We are writing in reference to an inspection by the Food and Drug Administration (FDA) of your firm located in West Chester, Pennsylvania on May 11 through June 18, 2004. Your products, the Norian® XR Calcium Phosphate Bone Void Filler (Norian XR) and the Norian SRS Bone Void Filler (Norian SRS), are devices within the meaning of section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 321(h)) because they are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or because they are intended to affect the structure or any function of the body.

During the inspection referenced above, the FDA learned that your firm is marketing the Norian XR for new intended uses without approval or clearance from FDA in violation of the Act. We also found violations of the Medical Device Reporting regulation (21 CFR Part 803) and the Current Good Manufacturing Practice (CGMP) of the Quality System regulation (21 CFR Part 820). Each of these violations is discussed below.

A. Marketing the Norian XR for New Intended Uses Without Approval or Clearance

The Act requires that manufacturers of medical devices obtain marketing approval or clearance for their products from FDA before they may offer them for sale. This helps protect the public health by ensuring that new medical devices are shown to be both safe and effective or substantially equivalent to other devices already legally marketed in this country.

A review of our records shows that Synthes Spine obtained premarket notification [510(k)] clearance for the Norian XR (K023862) for the following intended uses:

> "Norian® XR Calcium Phosphate Bone Void Filler is intended only for bony voids or defects that are not intrinsic to the stability of the bony structure. Norian® XR Calcium Phosphate Bone Void Filler is intended to be placed or injected into bony voids or gaps of the skeletal system (i.e.,

the extremities, spine and pelvis). These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. The product provides a bone void filler that resorbs over a period of years and is replaced with bone during the healing process."

The labeling for the cleared use of Norian XR also includes a warning that specifically states that the device is "[n]ot intended for treatment of vertebral compression fractures," and that "[h]ighly pressurized application of Norian XR into a tightly confined space with ready venous or arterial access is not recommended, as the potential for formation of emboli is unknown."

The following materials, all of which relate to the "[redacted]sored by Synthes Spine, were collected and reviewed during the inspection. Our [redacted]ew of these materials indicates that you are marketing the Norian XR for uses that are not within its cleared indications:

- Synthes Spine personnel made presentations to surgeons during training forums for potential participants in the [redacted]. These presentations included discussions of the use of Norian XR for vertebroplasty and kyphoplasty in association with the treatment of vertebral compression fractures.

- Guest surgeons made presentations during training forums sponsored by your firm for surgeons participating in the [redacted]. These presentations -- for example, the keynote address presented by [redacted]at the training forum in Charlotte, N.C. -- discussed use of the Norian XR for off-label indications, including vertebroplasty.

- Synthes Spine provided packets of information and compact discs (CDs) to surgeons who attended the training sessions. These materials included abstracts of papers describing uses of bone void fillers in vertebroplasty and kyphoplasty procedures, which would be considered off-label uses for Norian XR.

- Your firm developed the "[redacted]and distributed it to surgeons participating in the [redacted]for the purpose of collecting information. These forms capture data pertinent to uses of the Norian XR for vertebroplasty and kyphoplasty procedures for treatment of vertebral compression fractures. For instance, the form includes data entry sections for the age of the fracture, the level of fracture treated, and the percent compression. This type of data is specific to the treatment of vertebral compression fractures and is not general clinical data that would be collected for treatment of other spinal indications where the device is used for voids or defects not intrinsic to the stability of the bony structure.

Promotion of the Norian XR for vertebroplasty and kyphoplasty constitutes significant modifications to the intended uses of Norian XR, and therefore requires a new premarket notification submission prior to marketing your device for these new intended uses [21 CFR 807.81(a)(3)(ii)]. Moreover, because the [redacted] was a study conducted to determine the safety and effectiveness of using the Norian XR in a manner not cleared by FDA, you were required to have an FDA-approved Investigational Device Exemption (IDE) before you could legally conduct the Test Market [21 CFR 812.20(a)(2)].

Your promotion of the Norian XR and introduction of this device into interstate commerce for new intended uses is a violation of the law. Specifically, this device is adulterated under section 501(f)(1)(B) of the Act because you do not have an approved application for premarket approval (PMA) in effect pursuant to section 515(a) of the Act, or an approved application for an IDE under section 520(g) of the Act. The device is also misbranded under section 502(o) of the Act because you did not notify the agency of your intent to introduce the device into commercial distribution, as required by section 510(k) of the Act. For a device requiring premarket approval, the notification required by section 510(k) of the Act is deemed satisfied when a PMA is pending before the agency [21 C.F.R. 807.81(b)]. The kind of information you need to submit in order to obtain clearance or approval is available through the Internet at http://www.fda.gov/cdrh/devadvice/3122.html. The FDA will evaluate this information and decide whether your product may be legally marketed.

We acknowledge receipt of your responses dated July 7, 2004 and August 18, 2004. In your response dated July 7, 2004, Mr. James K. McCracken contends that your firm "did not ship product for indications that had not been approved or cleared by the FDA." In support of this contention, Mr. McCracken presents general definitions for vertebroplasty and kyphoplasty. The definition for vertebroplasty presented by Mr. McCraken is "the shaping or fixing of a vertebral body." The definition he presents for kyphoplasty is "one form of vertebroplasty specifically employing the use of an inflatable bone tamp for creating a void within the vertebral body which can be filled with some orthopedic cement or bone void filler." Your response does not acknowledge that the shaping of the vertebral body is to augment its structural integrity -- which is considered to provide stability to the bony structure.

The definitions of vertebroplasty and kyphoplasty provided by Mr. McCraken in the July 7 response do not represent the meaning of vertebroplasty and kyphoplasty in the context of use of a bone void filler like Norian XR, nor are they the common medical usage of these terms. Vertebroplasty is generally understood to mean the percutaneous injection of polymethylmethacrylate (PMMA) or other bone void filler into the vertebral body, to mechanically augment the weakened vertebral body after a compression facture. The term "compression fracture" means a fracture in which the bone collapses, especially in short bones such as vertebrae. The compression fractures treated by vertebroplasty are commonly the result of osteoporosis, but may also be caused by bone destruction by an osteolytic tumor or other conditions that weaken the bone. Vertebroplasty is used to reinforce the bone, preventing further collapse, and to relieve pain, most probably by eliminating fracture instability. Vertebroplasty for treatment of compression fractures in

the conditions described above and other conditions would therefore not be included within the cleared intended uses for Norian XR.

Vertebroplasty may be used to fill voids created by tumors such as hemangiomas. In these cases, the vertebrae may not have collapsed, but the purpose of these procedures is to reinforce or structurally augment the bone, with accompanying pain relief believed to result from splinting of trabecular microfractures. Vertebroplasty may also be used for prophylaxis in vertebrae at risk of collapse to prevent fracture and would also qualify as mechanical augmentation of the vertebral body. Since the voids being filled are intrinsic to the stability of the bony structure, vertebroplasty for the treatment of such conditions is also not within the intended uses for which Norian XR was cleared.

Kyphoplasty, as the term is commonly understood, is a specific procedure primarily used for reduction and stabilization of compression fractures, and the void that is filled is intrinsic to the stability of the bony structure. Kyphoplasty may also be used in patients with vertebral body involvement from neoplastic disease processes such as plasmocytoma or multiple myeloma. Use of kyphoplasty for these conditions is also considered intrinsic to the stability of the bony structure. Therefore, kyphoplasty is not within the cleared intended uses for the Norian XR.

In your July 7 response, Mr. McCracken also contends that your firm did not need an IDE to conduct the [redacted] because the intent of the [redacted] was to "gather customer feedback on the use and performance" of the Norian XR. However, based on our review of the [redacted] referenced above, we conclude that the [redacted] did in fact collect safety and effectiveness data regarding the Norian XR. Physicians participating in the [redacted] were required to complete the form, which was developed by Synthes Spine and distributed to surgeons participating in the [redacted] for the purpose of collecting data. The form required, among other information, data regarding the patients' pre- and post-operative pain, a statement of complications (including cement leakage) during the procedure, an explanation as to how complications were handled, whether postural reduction was attempted, and if so, the percentage of reduction achieved. The form also asked the physicians to provide copies of pre- and immediate post-operative x-rays. The collection of this data indicates that the [redacted] did in fact determine the "safety and effectiveness" of the Norian XR. Accordingly, an approved application for an IDE was required.

Mr. McCracken further contends in the July 7 letter that an IDE was unnecessary because the [redacted] "was done to develop information regarding on label uses of" the device. However, as discussed in more detail above, we have concluded that the [redacted] involved promotion of the Norian XR and introduction of this device into interstate commerce for new intended uses for which you do not have clearance or approval from FDA.

B. Medical Device Reporting

Our inspection also revealed that the Norian XR and Norian SRS are misbranded within the meaning of section 502(t)(2) of the Act (21 U.S.C. 352(t)(2)) because your firm failed to submit information to the FDA as required by the Medical Device Reporting (MDR) regulations set forth at 21 CFR Part 803. These regulations implement certain provisions of section 519 of the Act. Significant violations include, but are not limited to, the following:

1. The firm failed to submit an MDR report within thirty days of becoming aware of a patient death on January 13, 2003. The patient had received injections of Norian SRS that had been mixed with [redacted] in a vertebroplasty procedure for treatment of vertebral compression fractures [redacted] [21 CFR 803.50(a)(1)].

   In your July 7 letter, Mr. McCraken indicates that an MDR was not submitted for this report of death because the surgeon stated that the incident was not the result of the product or the procedure. Mr. McCraken also references 21 CFR 803.20(c)(2). We believe that this justification is inadequate. You seem to rely strictly on the physician's statement that he did not attribute the death to the product. However, the final responsibility for determining reportability rests with the manufacturer, taking into account a variety of information, including, but not limited to, device history files, complaint tracking, scientific, technical and clinical literature, internal investigations, and quality assurance programs. It is not enough that the device user did not attribute the adverse event to the use of the device. In addition, there was no information in the MDR file regarding why the qualified person determined that the event was not reportable, as required by 21 CFR 803.20(c)(2), nor was there any information as to why this event was not potentially device related.

   We acknowledge that you have revised Work Instruction [redacted] to require review of prior complaint history for the part family to determine if an event is MDR reportable. However, we recommend that you further amend your work instruction to require adequate investigation of an event that takes into account the other sources of information known to the firm listed above that may indicate that the device could have contributed to the serious injury or death. The work instruction should make clear that the final responsibility for determining reportability should not be solely based on the user facility's conclusions, but must take into account additional information known by the firm (e.g., similar reports, animal and clinical data, other scientific and technical data or literature). 21 CFR 803.17(a)(2) requires a standardized review process/procedure for determining when an event meets the criteria for reporting under Part 803.

2. You also failed to report supplemental information as required by 21 CFR 803.56, which provides that when "a manufacturer obtains information *required under this*

part that was not provided because it was not known or was not available when the initial report was submitted, the manufacturer shall submit to FDA the supplemental information within 1 month." (emphasis added). The information that manufacturers are required to submit under Part 803 is set forth at 21 CFR 803.52.

You did not report relevant medical information that was received after a Medical Device Report, MDR # 2939274-2004-05, was submitted to the FDA regarding the death of a patient. Specifically, review of the case file for MDR # 2939274-2004-05 revealed that there was an [redacted] report that your firm received by facsimile transmission on March 23, 2004, but that you did not submit a supplemental report based on the information in the [redacted]

The final [redacted] diagnosis given in the [redacted] report states the following: "[redacted]" In addition, there are details of the patient's [redacted] decreasing after injection with Norian XR.

Although the report was inconclusive as to whether or not this finding was associated with the patient's circulatory collapse, this information is reportable under 21 CFR 803.52(b)(5) and/or 803.52(b)(6). Moreover, the additional findings reported in the [redacted] report are similar to symptoms noted in previous animal studies as well as other MDR reports. Hence, FDA believes that such information should have been reported as a supplemental MDR, as required by 21 CFR 803.56. Please provide this information as a supplemental report to MDR 2939274-2004-05.

The justification submitted in your July 7, 2004, letter regarding why you did not submit a supplemental MDR report for MDR 2939274-2004-05 is insufficient. Mr. McCraken indicates that you did not submit a supplemental report because the [redacted] report was inconclusive and you did not believe that there was a need to alter information submitted in the original MDR report based on the information from the [redacted] report. Mr. McCraken indicates that this decision was based on a Department of Health and Human Services guidance document entitled, "Medical Device Reporting for Manufacturers," dated March 1997. We agree that the guidance document states that a supplemental report is not required if the new information does not change the facts and/or conclusion reported in the original MDR report. However, in this case the [redacted] report changed the facts as reported in the initial MDR because it provided additional clinical information indicating that the Norian XR possibly migrated from the implant site.

We acknowledge that you have revised Work Instruction document [redacted] to require that the firm file a supplemental report whenever additional information is received. According to [redacted] a supplemental report is required "[redacted]" or "[redacted]

[redacted] This portion of your response appears to be inadequate because the work instruction does not provide criteria on how to determine if new facts may alter the previously submitted information even if the new facts appear to be inconclusive.

3. You failed to include in your MDR event files information in your possession or references to information related to the adverse event and all documentation of your deliberations and decision making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable, as required by 21 CFR 803.18(b)(1)(i). For example, the record of investigation of MDR 2939274-2004-01 for a report of the explantation of Norian SRS from a patient treated for a calcaneus fracture did not contain the date and results of a telephone conference that had occurred between the reporting surgeon, the Complaint Handling Unit (CHU) representative, and the firm's medical consultant.

   In your response dated July 7, 2004, Mr. McCraken indicates that Work Instruction [redacted] has been revised to require the documentation of conversations associated with complaint and MDR investigations and to maintain those documents on file, and that retraining has been completed. Your response appears to be adequate.

C. Quality System Regulation

Our inspection also revealed that your medical devices appear to be adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)) in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at 21 CFR Part 820. Significant violations include, but are not limited to, the following:

Failure to maintain procedures for receiving, reviewing, and evaluating complaints by the formally designated complaint unit, as required by 21 CFR 820.198(a). Specifically, a number of product quality complaints and adverse event reports received during the Norian XR [redacted] and [redacted] were not reported to the firm's CHU for evaluation as required by Synthes Work Instruction entitled, [redacted]

In your July 7 response, Mr. McCraken acknowledges that the Synthes Work Instruction was not followed. He indicates that notifications were sent by mail to all employees reinforcing the requirements in [redacted] and that Product Development personnel have received formal retraining on this work instruction. Mr. McCraken also conveys that you will require that all employees receive formal retraining on [redacted] all employees will be retrained periodically, and compliance audits will be performed on documents with feedback from the field. We acknowledge that you revised Work Instruction [redacted] to include this new requirement.

Your response may be adequate; however, please indicate whether or not the previous complaints noted on the FDA-483 have been forwarded to the firm's CHU, documented, and adequately investigated.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt action to correct the violations and to bring your products into compliance.

These serious violations of the law may result in the FDA taking regulatory action against you without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Federal agencies in the U.S. are informed about the Warning Letters we issue, such as this one, so that they may consider this information when awarding U.S. government contracts.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include all documentation of the corrective action you have taken. If you plan to make any corrections in the future, include those plans with your response to this letter as well. Please direct your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement B, Orthopedic, Physical Medicine, and Anesthesiology Devices Branch (HFZ-343), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Ms. Pamela D. Scott.

If you have more specific questions concerning GMP/QSR and MDR issues, how FDA marketing requirements affect your particular device, or about the content of this letter,

please feel free to contact Ms. Pamela D. Scott at (301) 594 – 4659. You may also contact Dr. Jean Toth-Allen at (301) 594-4723 for any questions concerning bioresearch monitoring and conduct of a clinical study.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc: Michael D. Huggins
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